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Self-assembled nanoformulation of methylprednisolone succinate with carboxylated block copolymer for local glucocorticoid therapy

Marat I. Kamalov[a], Trinh Đặng[a], Natalia V. Petrova[a], Alexander V. Laikov[a], Duong Luong[a], Rezeda A. Akhmadishina[a], Andrei N. Lukashkin[b], Timur I. Abdullin[a,*]

[a] Institute of Fundamental Medicine and Biology, Kazan (Volga Region) Federal University, 18 Kremlyovskaya St., 420008 Kazan, Russia
[b] School of Pharmacy and Biomolecular Sciences, University of Brighton, Brighton BN2 4GJ, UK

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ABSTRACT

A new self-assembled formulation of methylprednisolone succinate (MPS) based on a carboxylated trifunctional block copolymer of ethylene oxide and propylene oxide (TBC-COOH) was developed. TBC-COOH and MPS associated spontaneously at increased concentrations in aqueous solutions to form almost monodisperse mixed micelles (TBC-COOH/MPS) with a hydrodynamic diameter of 19.6 nm, zeta potential of −27.8 mV and optimal weight ratio ~1:6.3. Conditions for the effective formation of TBC-COOH/MPS were elucidated by comparing copolymers and glucocorticoids with different structure. The micellar structure of TBC-COOH/MPS persisted upon dilution, temperature fluctuations and interaction with blood serum components. TBC-COOH increased antiradical activity of MPS and promoted its intrinsic cytotoxicity *in vitro* attributed to enhanced cellular availability of the mixed micelles. Intracellular transportation and hydrolysis of MPS were analyzed using optimized liquid chromatography tandem mass spectrometry with multiple reaction monitoring which showed increased level of both MPS and methylprednisolone in neuronal cells treated with the formulated glucocorticoid. Our results identify TBC-COOH/MPS as an advanced *in situ* prepared nanoformulation and encourage its further investigation for a potential local glucocorticoid therapy.

1. Introduction

Glucocorticoids are adrenal cortex derived, natural and semisynthetic steroid hormones with pleiotropic biological activities in mammals [1]. They include cortisol (hydrocortisone), a primary endogenous hormone, and a range of its synthetic derivatives, such as dexamethasone, prednisolone, methylprednisolone and their ethers. Glucocorticoids are one of the most frequently used therapeutics with versatile effects on metabolic processes, pronounced anti-inflammatory, immunomodulatory, anti-allergic and anti-edema properties [1].

Besides routine use of glucocorticoids to treat widespread diseases, including allergies, asthma, autoimmune and degenerative disorders [1], they are also considered as emergency drugs administered in severe clinical cases, such as sepsis and acute neuronal traumas [2,3]. Methylprednisolone infusion therapy has been intensively studied in order to alleviate the consequences of acute spinal cord injuries which result from glutamate neurotoxicity and inflammation [3,4]. The neuroprotective action of glucocorticoids administered after hypoxia or traumatic injury was established [4–6]. This therapeutic effect is, however, observed within a relatively narrow range of concentrations, and increased drug levels could promote tissue degeneration [7].

The high therapeutic potential of glucocorticoids is accompanied by their intrinsic side effects, including immunosuppression, hypertension, osteoporosis, metabolic disturbances as well as decreased sensitivity upon repetitive administration [1]. Development of pharmaceutical approaches for reduction of these adverse effects is of considerable biomedical interest. The common strategy relies on the systemic use of glucocorticoids encapsulated into liposomal or micellar nanocarriers designed for increasing solubility and pharmacokinetic profile of the drugs [6,8]. Localized delivery of glucocorticoids to target tissues could provide substantial advantages over systemic administration. The advantages are related to improved safety and sustained therapeutic dose level. Localized therapy should be based on an effective delivery system, incorporating medical devices, carriers and/or penetration enhancers. The delivery systems are mainly designed to increase local bioavail-

* Corresponding author.
E-mail addresses: tabdulli@gmail.com, timur.abdullin@kpfu.ru (T.I. Abdullin).

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